Working for Women's Health

Women's health is an area that is gaining increasing attention with the realization that men's and women's bodies don't just look different—they also react differently to environmental agents. Barbara J. Davis, head of the Female Reproductive Pathology Group and now acting chief of the newly created Laboratory of Women's Health, is leading women's health studies at the NIEHS. Over the course of her 10 years at the institute, Davis has concentrated her efforts on studying ovarian toxicity and its relationship to the environment.

The ramifications of infertility stretch further than just whether a woman can bear children. For instance, in addition to making a woman less likely to conceive, persistently lower estrogen concentrations have been shown to contribute to osteoporosis and heart disease. Davis urges a broad perspective in looking at women's health, a perspective that takes into account not just the primary effects but also the secondary and tertiary effects of a particular exposure.

Davis's strategy has been to develop rodent models that mimic the human menstrual cycle so that she can study the effects of chemical exposures over several iterations of a hormonal cycle. Rather than inundate the model with a chemical that totally shuts down the reproductive system, she says, she leaves the reproductive system intact so as to study the long-term effects of certain exposures. Davis feels that the cyclical approach taken toward women's diseases could also be applied to male-specific hormone-related diseases such as prostate cancer.

The Female Reproductive Pathology Group provides support for reproductive toxicity studies conducted by the National Toxicology Program. The group studies the pathophysiology of ovarian dysfunction and cancer in women and rodents caused by chemical exposures, and seeks to identify ovarian target cells as well as the biochemical and molecular mechanisms by which both synthetic and naturally occurring environmental chemicals cause ovarian dysfunction or cancer. Both *in vivo* and *in vitro* models are used in this work. The group is also working to determine the role of key genes and signaling molecules in ovarian cell growth, differentiation, and physiology, and to understand how to modify these pathways to prevent or lessen the chance of ovarian dysfunction and cancer. The Laboratory of Women's Health is expected to carry those studies a step further, extending them into the realm of human exposure.

Ovarian Toxicity

Ovarian toxicity refers to the ways that different chemicals affect the ovaries. Because the ovaries are a clearinghouse of hormonal activity in the female body, disruption of ovarian function greatly affects women's reproductive and endocrine health. If a chemical exposure affects ovarian function, it may eventually lead to any of several hormone- and aging-related dysfunctions, including infertility, birth defects, cancer, and osteoporosis.

According to Davis, many women's diseases tend to appear at certain times in a woman's life. For instance, osteoporosis is largely a disease of postmenopausal women while endometriosis affects women during their childbearing years. Davis wants to find out what changes occur in a woman's body over time that may make her either more or less susceptible to particular diseases as she ages.

Davis's work on adult ovarian function has centered around the effects of two classes of chemicals: phthalates and ethylene-based glycol ethers. Phthalates are used to make plastic flexible and soft. They are contained in cosmetic products such as nail polish and in paints, varnishes, or any plastic that needs to be flexible. Ethylene-based glycol ethers are primarily used as solvents and can be found in paints, varnishes, and deicing chemicals. They are also used in the semiconductor industry. The route of exposure for both types of chemicals may be dermal or inhalational. People are also exposed to phthalates orally as they leach from plastic products into food.

Davis says the data are not yet available to determine whether exposure to these chemicals constitutes a major health concern. "As phthalates represent one of the largest class of synthetic compounds produced, we need to be aware of their potential health effect and determine how they act and to what extent people really are exposed," she says. "We are only getting those data now."

According to Davis, although there is little research to date that strongly implicates phthalates as a reproductive toxicant in women, a few phthalates clearly affect the ovaries in rodents. Di(2-ethylhexyl) phthalate (DEHP), for instance, has been shown in rodents to suppress estradiol production. Estradiol circulating in the blood cues the pituitary gland to direct the ovaries to ovulate—without this cue, the direction never comes and the rodents fail to ovulate. Nevertheless, egg follicles are still developing in the ovaries; they just aren't being released. Instead, they stay in the ovaries, growing ever greater in number and possibly eventually turning into cysts. Davis says, "I don't believe DEHP is an ovarian carcinogen. But the effects of DEHP could lead to infertility."

Laboratory of Women's Health

Several epidemiological studies have shown ethylene-based glycol ethers to have reproductive effects. Glycol ethers have been shown to induce spontaneous abortion and possibly to reduce female workers' fecundability (ability to deliver a live birth), although fertility appears to be unaffected. In papers published in the February 1997 and August 1997 issues of *Fundamental and Applied Toxicology*, Davis and colleagues from the NIEHS Laboratory of Experimental Pathology and Duke University in Durham, North Carolina, studied the effects of ethylene glycol monomethyl ether and its metabolite methoxy acetic acid on ovarian luteal cells of rats and humans, respectively. They found that the chemicals elevated progesterone production in both rat and human cells. In the rats, the chemicals also inhibited ovulation. Davis and colleagues speculate that the chemicals may cause the same effect in humans.

The Role of COXs

Cyclooxygenases (COXs) are enzymes that produce various synthases of prostaglandins, which play a critical role in signaling ovarian function, ovulation, and luteal function. Along with colleagues in the Metabolism and Molecular Mechanisms Group within the NIEHS Laboratory of Environmental Carcinogenesis and Mutagenesis, Davis conducted studies to delineate the roles of COX-1 and COX-2 in reproductive function. The studies, published in the June 1999 issue of *Endocrinology*, used mice lacking the genes for either COX-1 or COX-2.

The investigators were able to determine that mice that lacked COX-2 failed to ovulate and had abnormal implantation and decidualization responses (the uterine changes that allow for implantation), whereas the COX-1–deficient mice were fertile. The studies also showed that the COX-1–deficient mice exhibited aberrant estradiol production and indicated that both prostaglandins and estradiol are necessary for normal delivery. Finally, the studies showed for the first time that ovulation can be

restored in COX-2–deficient mice by simultaneous treatment with gonadotropins and either the prostaglandin synthase PGE2 or the cytokine interleukin-1β, which may provide a clue to future infertility treatments.

These studies suggest that, contrary to traditional belief, it is COX-1 and not COX-2 that produces the prostaglandins that are necessary for boosting ovarian estradiol production, and that estradiol levels then determine the production of COX-2–related prostaglandins. Future studies will evaluate specific chemicals and their effect on ovarian function and interaction with prostaglandin pathways.

Pesticide Exposures

Along with Bob Chapin of the Reproductive Toxicology Group within the NIEHS Laboratory of Toxicology, Davis has studied the effects of pesticide exposures on juvenile and adult rodents. In a paper published in the November 1997 issue of *Fundamental and Applied Toxicology*, for instance, the pesticide methoxychlor was shown to cause ovarian dysfunction resulting in reduced estrous levels of follicle-stimulating hormone at all dosages and reduced estrous progesterone levels at some dosages. Davis has also studied the effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or dioxin), which has been shown to promote ovarian tumors in female rats, and nitrofurantoin, an antibiotic used for urinary tract infections that has been associated with ovarian cancer in rodents, although not in humans.

Davis and colleagues are currently working to understand how TCDD causes tumors to develop and whether women may be at risk from these exposures. One possible connection between the rodent and real human exposure is that the type of ovarian tumor induced by TCDD in the rats in Davis's experiments is the same histological subtype as that found in one young woman who had been exposed to dioxins during a 1976 industrial accident in Seveso, Italy. "Because this subtype of ovarian tumor is indeed rare and because tumors of any kind are rare at such a young age in women, it is possible that the appearance of the tumor in the Italian woman was related to the exposure," says Davis. "It is also possible this finding could have been a random and unrelated event. We clearly need to investigate and distinguish these possibilities."

The Laboratory of Women's Health

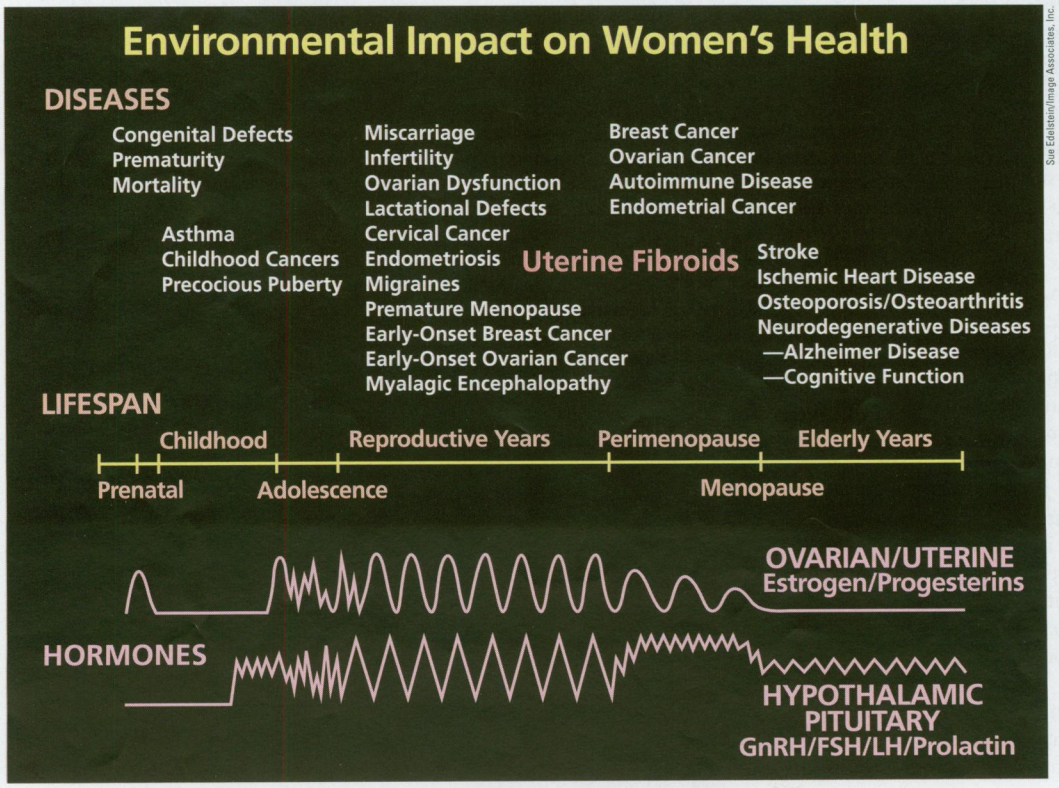
The Laboratory of Women's Health is part of the institute's Environmental Diseases and Medicine Program. Davis says it's one of the first intramural research facilities devoted to women's health in the NIH system. The lab is the brainchild of Davis and Carl Barrett, scientific director of the NIEHS and chief of the Laboratory of Molecular Carcinogenesis, who played a key role in its development. The lab will draw on the expertise of many different investigators to look at the big picture of women's health. "We really want to cross-talk," Davis says. "To be a good scientist, you need the environment to be creative, to talk. The lab will offer this environment."

Toxicity studies generally follow a progression from animal *in vivo* studies to target cell *in vitro* studies to human *in vitro* studies and finally to human *in vivo* studies. To date, Davis's work has progressed to human *in vitro* studies and, with the establishment of the new laboratory, she hopes to tackle the final stage, human *in vivo* studies. "One of the goals," says Davis, "is to get more translational work underway. We're really bridging that gap between toxicological studies and human exposure."

Specifically, the lab will build on work Davis and Roger Wiseman, a senior staff fellow in the lab's Comparative Carcinogenesis Group, have already started with the breast cancer susceptibility genes *Brca1* and *Brca2* as they relate to breast and ovarian health. (Despite the gene's name, *Brca1* mutations are also known to increase cancer susceptibility in the ovaries.) The lab will also expand its focus and search for key genes and signaling processes in the reproductive and immune systems and strive to define how environmental stresses and toxicants alter those processes and genes. Investigators will study ovarian function during pregnancy and childbirth, ovarian cancer, breast cancer, uterine leiomyomas (fibroid cysts), and autoimmune diseases. Ultimately, the lab's researchers hope to reduce the burden of environmentally related diseases in women through the combined effort and expertise of geneticists, endocrinologists, immunologists, pathologists, and epidemiologists.

To that end, Davis emphasizes the idea of a "virtual lab" in which scientists will have free and constantly updated access to an ever-expanding body of data and knowledge to be used as stepping stones and building blocks in collaborative research efforts. "We need to always be ready to evolve as we understand new concepts," Davis says.

Susan M. Booker



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